Blood Glucose and Schizophrenia: A Systematic Review of Prospective Randomized Clinical Trials

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Objective: Most of the data evaluating the potential relationship between diabetes, schizophrenia, and antipsychotics currently derive from retrospective analysis. Relevant confounders of such data include screening and selection bias. Prospective data collected from randomized controlled trials may reduce such biases. As no single trial has glucose comparisons as a primary endpoint, we undertook a systematic review of available data.

Data Sources: Embase, HealthStar, MEDLINE, Pre-MEDLINE, and PsycINFO databases were searched online for relevant articles. Abstracts from major congresses held between January 2000 and April 2006 were included. Search terms included all currently available antipsychotics: *olanzapine*, *risperidone*, *clozapine*, *quetiapine*, *ziprasidone*, *aripiprazole*, *haloperidol*, *chlorpromazine*, and *zotepine*.

Study Selection: Prospective clinical trials involving schizophrenia patients with no stated previous glucose abnormalities randomly assigned to cohorts receiving active or placebo comparator antipsychotic medications were included with no restrictions on study length. 16 studies were from peer-reviewed publications, 4 were from posters at major congresses, and 2 were available only on Internet-based sites.

Data Extraction: Glucose parameters reported included fasting and random glucose and glycosylated hemoglobin. Data reported included mean changes and categorical reports of abnormal levels.

Data Synthesis: Data were available in 6329 patients from 22 trials. The most common comparator agents were aripiprazole and olanzapine in 4 studies including 1432 patients. 14 studies reported fasting and 9 studies reported nonfasting data. 15 studies were a minimum of 5 months, with 8 studies of at least 1 year's duration. No consistent significant glucose differences were found between any comparator antipsychotics or placebo in any trial.

Conclusions: In contrast to some of the retrospective data, an analysis of prospective data from randomized clinical trials showed no consistent significant differences in the incidence of treatment-emergent glucose abnormalities in patients treated with antipsychotics. The reduction in both screening and selection biases may be relevant. Although one third of the studies had at least 1 year's duration, the data are not sufficient to reach conclusions regarding patients receiving longer-term treatment with atypical antipsychotics.

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The association between diabetes mellitus type 2 and schizophrenia has been recognized for over 100 years.[1,2] There is general consensus that schizophrenia patients develop diabetes mellitus type 2 more commonly than the general population.[3,4] This association clearly predates the development of the antipsychotics that are used for the long-term treatment and prevention of relapse in schizophrenia.[2]

There has been debate over whether treatment with antipsychotics may potentially increase the risk of diabetes in schizophrenia patients and whether the potential risk is greater during treatment with atypical antipsychotics as a class or with certain antipsychotics. The majority of data reported to help clarify these issues derive from predominantly retrospective data sets.[5–7] Interpretation of these data sets is confounded by the nature of diabetes mellitus type 2, which is essentially in most cases an asymptomatic disease.[8] Retrospective data by definition derive from databases that were not specifically designed to address comparisons of the association of diabetes mellitus type 2 and various antipsychotics.[9] Due to the inability of these databases to assess the numbers of individual patients who have undergone glucose testing on the various antipsychotics, there remains the possibility that any conclusions drawn might reflect, at least partially, the known fact of patients taking certain antipsychotics such as clozapine and olanzapine having more glucose testing.[10,11] Examples of such types of database include case reports and series, pharmacovigilance data, cross-sectional prevalence studies, and cohort comparisons using matched controls. A further confounder could be that in many countries, atypical antipsychotics were not easily available during the period of these reported studies and that some of the more recently introduced atypicals had not yet been licensed. Hence, significant potential confounders exist, including

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screening bias and selection bias, that need to be addressed.[12] Most of the retrospective epidemiology studies also lack data on important diabetes risk factors, such as a family history of diabetes, baseline glucose, and baseline body mass index.[9]

The increasing emphasis on evidence-based medicine has led to a number of hierarchies of levels of evidence being proposed. In general terms, the highest level of evidence derives from properly conducted prospective randomized controlled trials (RCTs). These trials reduce the likelihood of significant bias by randomly assigning patients and requiring equal protocol-specific rates of glucose testing in the cohort subjects. To our knowledge, glucose endpoints have not been the primary endpoint in any RCT reported in the literature comparing antipsychotics in schizophrenia patients. Despite this caveat, glucose data are in many cases routinely collected during phase 2 and 3 clinical trials that are designed to provide safety data to a regulatory authority prior to licensing and more recently have been incorporated into other clinical trials involving antipsychotics. During the last few years, newly licensed atypical antipsychotics (aripiprazole and ziprasidone) have been given regulatory approval in various countries. Hence, we undertook a systematic review to determine the extent of currently available glucose data that derived from prospective RCTs and the length of follow-up. The natural history of diabetes mellitus type 2 often has a lag time of 5 to 10 years before overt hyperglycemia is measured, and to provide critical evidence of any putative association between medication and glucose, due for instance to weight gain, such trials would need to be long term.[3]

METHOD

Data Sources and Study Selection

A literature search was conducted to identify prospective randomized clinical trials in schizophrenia that included cohorts taking different antipsychotics in which glucose parameters could be compared longitudinally. There were no restrictions on study length. These publications were further examined to extract any published data pertaining to plasma glucose measurements. Search terms included all currently available antipsychotics: *olanzapine*, *risperidone*, *clozapine*, *quetiapine*, *ziprasidone*, *aripiprazole*, *haloperidol*, *chlorpromazine*, and *zotepine*. Embase, HealthStar, MEDLINE, Pre-MEDLINE, and PsycINFO databases were searched online for relevant articles, and psychiatric conference abstracts and posters from meetings of the American Psychiatric Association, European College of Neuropsychopharmacology, International Congress on Schizophrenia Research, British Association for Psychopharmacology, and Schizophrenia Winter Workshops between January 2000 and April 2006 were examined. Data published at a later date that add to these original data have also been included.[13]

Searches were also conducted for Internet-based data, for example, the U.S. Food and Drug Administration (FDA) Web site. Internet journals and journals that are not linked through Index Medicus were also sourced. Clinical trial reports were also sourced from Internet-based sites where antipsychotic-related trials in schizophrenia had been published.

Data Extraction

All glucose parameters were examined. Parameters included fasting glucose, random glucose, insulin levels, and glycosylated hemoglobin (HbA_{1c}). In some cases in which the glucose data were reported in a publication separate from the primary study, the relevant primary study details were accessed from a different source. Studies were excluded when patients at study entry had existing known diagnoses of any significant glucose abnormality as in Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[14] Insulin levels are reported additionally.

Statistical Analysis

The disparate nature of the glucose data and the various different parameters used did not allow the data to be reviewed in the traditional format of a meta-analysis. No additional statistical analysis has been performed. The statistical calculations from the source data are reported where appropriate.

RESULTS

A total of 22 prospective RCTs were identified as including glucose parameters in which a minimum of 2 antipsychotic agents (or placebo) were compared and data had been reported (Table 1).[13,15–34] Most studies were reported as peer-reviewed clinical articles (16 publications) or posters at major international and national congresses (4 publications). Internet sites that are freely accessible to clinicians and the general population provided data from 2 RCTs and contributed further data to an additional RCT. In 2 studies, data are reported at 2 separate time points.

Glucose data were reported as fasting in 14 data sets and as nonfasting in 9 (Table 1). In 1 study, HbA_{1c} levels were the only data reported. Insulin data are reported in 3 study reports, of which 2 derive from the same study at different time points. In 1 study, data were reported on both random and fasting glucose. A number of varying glucose endpoints were reported. Mean glucose changes from baseline to endpoint between antipsychotic cohorts are most commonly reported. In addition, categorical data points including numbers of patients whose glucose levels became elevated to greater than 6.1 mmol/L (fasting) or greater than 11.1 mmol/L (nonfasting) are also reported. In 3 studies, HbA_{1c} levels are reported. In some studies, the

Table 1. Clinical Trials Providing Data on Glucose Parameters Included in Systematic Review

Study	Drug 1	Drug 2	Trial Summary	Glucose Data
Simpson et al (2004)[15]	Ziprasidone (N = 136)	Olanzapine (N = 133)	6-week RCT in schizophrenia. Primary endpoint: BPRS and CGI. No between-group differences. Increases in lipids and weight in olanzapine cohort	Fasting glucose unchanged in both cohorts. Median change from baseline of 1 mg/dL in both cohorts. Olanzapine increased insulin levels, difference between groups p = .051
Kane et al (2003)[16]	Ziprasidone (N = 271)	Olanzapine (N = 277)	28-week RCT in schizophrenia. Primary endpoint: PANSS. Olanzapine superior in PANSS (p < .001) and response rate (p < .001)	Mean change in fasting glucose from baseline: 0.26 (SD = 1.67) mmol/L for olanzapine and 0.00 (SD = 1.20) mmol/L for ziprasidone (p = .485)
Lieberman et al (2003)[17]	Haloperidol (N = 132)	Olanzapine (N = 131)	12-week RCT in first-episode psychosis. Mixed-model analysis: olanzapine superior in PANSS total and MADRS only, less EPS; greater weight gain for olanzapine and lower discontinuation rates (haloperidol = 67% vs olanzapine = 54%)	Mean change in nonfasting glucose from baseline: 4.9 (SD = 34.24) mg/dL for olanzapine and –3.33 (SD = 22.84) mg/dL for haloperidol (p = .21)
McQuade et al (2004)[18]	Aripiprazole (N = 156)	Olanzapine (N = 161)	26-week RCT in schizophrenia, acute relapse and hospitalized. Primary endpoint: number of patients gaining > 7% body weight (olanzapine = 37% vs aripiprazole = 14%; p < .001)	Mean change in fasting glucose from baseline to endpoint: no significant differences; 5 mg/dL for aripiprazole and 7 mg/dL for olanzapine
Bushe and Leonard (2004)[19]	Aripiprazole (N = 128)	Olanzapine (N = 127)	26-week randomized, open-label in schizophrenia. Primary endpoint: cognitive function. Weight gain: olanzapine mean increase = 3.6 kg, aripiprazole mean decrease = 0.9 kg	Increase from baseline of nonfasting glucose from < 8.8 mmol/L to > 11.1 mmol/L: 4.5% of olanzapine and 4.7% of aripiprazole patients
Marder et al (2003)[24]	Placebo (N = 309) Haloperidol (N = 182)	Aripiprazole (N = 648)	Review of pooled safety analysis of five 4- to 6-week RCTs in schizophrenia, acute relapse and hospitalized. Aripiprazole adverse event rate similar to placebo and less than haloperidol	Incidence of nonfasting glucose < 8.8 mmol/L increasing to > 11.1 mmol/L: 1.4% of aripiprazole and 1.3% of placebo patients
Marder et al (2003)[24]	Placebo (N = 34)	Aripiprazole (N = 120)	6-week RCT reports glucose data on partial cohort only (27%–35% of subjects). Aripiprazole safety parameters similar to placebo	Fasting glucose "above normal": 6% of aripiprazole and 10% of placebo patients. Mean baseline change: 0.021 mmol/L for aripiprazole and 0.279 mmol/L for placebo
Simpson et al (2005)[32]	Ziprasidone (N = 55)	Olanzapine (N = 71)	104-week RCT. Primary endpoint: BPRS and CGI. Comparable efficacy. Increased lipids and weight in olanzapine cohort	Fasting insulin: no between-group differences. Within olanzapine cohort, median baseline increase of insulin (p = .003)
Green et al (2006)[31]	Olanzapine (N = 131)	Haloperidol (N = 132)	2-year outcome data on the Lieberman et al 2003 study[17] 12-week data. Multiple efficacy endpoints. Similar reductions in symptom severity. Olanzapine superior on treatment discontinuations and EPS and inferior with weight, liver function, and cholesterol	Weight gain > 7%: 72% of olanzapine and 42% of haloperidol patients. Nonfasting glucose "similar" in study completers
Stock et al (2005)[25a]	Aripiprazole (N = 80)	Olanzapine (N = 85)	52-week randomized, open-label comparing efficacy, safety, and metabolic profile. No difference in PANSS. Lipids elevated in olanzapine cohort	Weight gain > 7%: 24% of olanzapine and 10% of aripiprazole patients. Mean change in fasting glucose from baseline: 12.02 mg/dL for olanzapine and –1.44 mg/dL for aripiprazole (p = NS)
Vanelle and Douki (2004)[29]	Olanzapine (N = 40)	Amisulpride (N = 45)	8-week RCT in schizophrenia and comorbid depression. Weight and metabolic parameters. Trend for increased lipids in olanzapine cohort. Mean weight change: –0.5 kg for amisulpride, 1.45 kg for olanzapine	Fasting glucose: no significant difference; –0.53 mmol/L for amisulpride and 0.13 mmol/L for olanzapine. No abnormal values
Smith et al (2005)[28]	Olanzapine (N = 10)	Risperidone (N = 10)	21-week RCT in schizophrenia. Fasting metabolic parameters. Preliminary results include oral glucose tolerance test data	Elevated insulin (p < .05) in olanzapine cohort. No differences in glucose but trend in both cohorts for elevation (p < .03). Oral glucose tolerance test: no differences in glucose or insulin

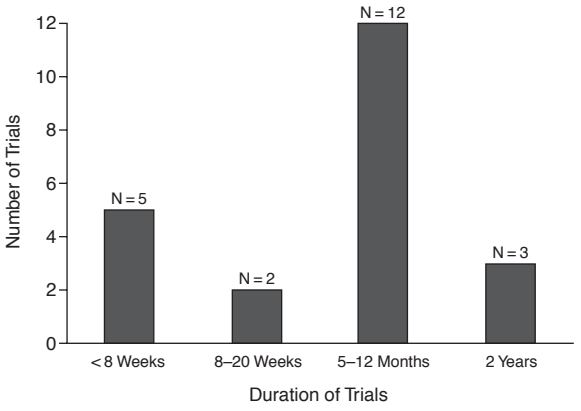
(continued)

Table 1 (continued). Clinical Trials Providing Data on Glucose Parameters Included in Systematic Review

Study	Drug 1	Drug 2	Trial Summary	Glucose Data
Bushe et al (2007)[33]	Olanzapine (N = 171)	Quetiapine (N = 175)	6-month RCT to assess efficacy in predominantly negative symptom schizophrenia subjects. Primary endpoint: SANS—no group differences. Secondary endpoints favored olanzapine: discontinuations, positive symptoms, and quality of life	No differences in any parameter: weight, lipids, or glucose. Mean change in nonfasting glucose: 0.75 mmol/L for olanzapine and 0.13 mmol/L for quetiapine (p = .250)
Lindenmayer et al (2003)[21]	Olanzapine (N = 26) Risperidone (N = 22)	Haloperidol (N = 25) Clozapine (N = 28)	14-week RCT in acute schizophrenia inpatients. 8-week fixed dose and 6-week variable dose. Increases in cholesterol in olanzapine and clozapine cohorts. Mean olanzapine dose = 31.4 mg	Abnormal glucose > 125 mg/dL in 14% taking all antipsychotics at 14 weeks. Trend for olanzapine only of increased fasting glucose after 14 weeks (p < .02)
Lieberman et al (2003)[20]	Clozapine (N = 80)	Chlorpromazine (N = 80)	52-week RCT in first-episode schizophrenia in China. Primary endpoint: time to remission. No difference at 52 weeks in numbers in remission but clozapine faster and longer	No significant difference in fasting glucose
Torbeyns et al (2004)[22]	Placebo (N = 108)	Aripiprazole (N = 113)	26-week RCT of relapse prevention in stable schizophrenia subjects. Aripiprazole superior to placebo	Fasting glucose > 6.1 mmol/L in around 20% of each cohort. No exact figures provided
Beasley et al (2003)[23]	Olanzapine (N = 224)	Placebo (N = 102)	52-week RCT of relapse prevention in schizophrenia outpatients. Primary relapse criteria: BPRS or hospitalization. Longer time to relapse in olanzapine (p < .0001): 5.5% vs 55% for placebo at 6 months	Nonfasting glucose levels not > 200 mg/dL in any subjects
Emsley et al (2005)[27]	Quetiapine (N = 22)	Haloperidol (N = 23)	52-week RCT. Primary endpoints: change in body mass index and HbA_{1c}	No between-group differences in body mass index or HbA_{1c}
Study CN 138003 (2005)[26]	Aripiprazole (N = 355)	Olanzapine (N = 340)	52-week RCT in non-inferiority acute schizophrenia. Primary endpoints: PANSS, weight change > 7%, and discontinuation rates. Olanzapine superior for PANSS and discontinuation rates at 6 and 52 weeks	Weight gain > 7%: 42% of olanzapine and 18% of aripiprazole patients. Fasting glucose and HbA_{1c} decreased in both cohorts
Meltzer et al (2003)[30]	Clozapine (N = 490)	Olanzapine (N = 490)	2-year RCT in schizophrenia subjects at high risk of suicide. Less suicidal behavior in clozapine patients (hazard ratio = 0.76)	Diabetes: 3.3% of clozapine and 4.4% of olanzapine patients (p = .41)
Chrzanowski et al (2006)[13a]	Aripiprazole (N = 80)	Olanzapine (N = 85)	52-week open-label extension RCT of efficacy and safety. No difference in PANSS or EPS. Greater weight gain in olanzapine, 2.54 kg vs 0.04 kg in aripiprazole (p < .001), and greater lipids (except triglycerides). Body weight gain > 7% greater for olanzapine than aripiprazole (24% vs 10%; p = .008)	Fasting glucose (p = NS): –1.4mg/dL for aripiprazole and 12.0 mg/dL for olanzapine. Categorical "significant" levels in 27% of olanzapine and 16% of aripiprazole patients (p = .127). Minimal HbA_{1c} change with either treatment
Kinon et al (2006)[34]	Olanzapine (N = 202)	Ziprasidone (N = 192)	24-week RCT of schizophrenia subjects with prominent depressive symptoms. Greater improvement and lower discontinuation rate in olanzapine subjects (p = .003)	Olanzapine-treated patients experienced significantly (p < .05) greater increases in triglycerides, HbA_{1c} (mean change of 0.06 for olanzapine and –0.06 for ziprasidone), and weight. No difference in fasting glucose; mean change from baseline: 2.85 mg/dL for olanzapine and 0.14 mg/dL for ziprasidone. Categorical rates of treatment-emergent high values did not differ: HbA_{1c} (olanzapine = 5.3%, ziprasidone = 2.5%; p = .337) and fasting glucose (olanzapine = 1.7%, ziprasidone = 2.3%; p = 1.0)

[a]Stock et al.[25] data, from a poster, are the same as the data published in Chrzanowski et al.[13] The numbers have been counted only once.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, EPS = extrapyramidal symptoms, HbA_{1c} = glycosylated hemoglobin, MADRS = Montgomery-Asberg Depression Rating Scale, NS = not significant, PANSS = Positive and Negative Syndrome Scale, RCT = randomized controlled trial, SANS = Scale for the Assessment of Negative Symptoms.

Figure 1. Duration of Trials Providing Data on Glucose Parameters



percentage of patients with "categorical significant" glucose abnormalities are reported without further being defined.

The lengths of the studies are shown in Figure 1 and Table 1. Fifteen studies were a minimum of 5 months, with 8 studies of at least 1 year's duration and 3 studies reporting 2-year data (Figure 1). Data are reported on 9 antipsychotics and placebo cohorts totaling 6329 patients (Figure 2). The majority of patients were receiving aripiprazole, olanzapine, clozapine, ziprasidone, or placebo.

Glucose data are not reported on the complete cohort in some studies. No details are provided in the publications regarding the demographics of the sampled versus the nonsampled patients nor the reasons for nonsampling. The study cohorts range from 20 patients to 1139. The mean cohort size was 349 (SD = 319); median = 263. In 4 of the 22 studies, the cohort size was greater than 500 patients, and in only 3 of the 22 studies was the cohort size below 100.

No significant glucose differences were reported in the 22 RCTs between any of the comparative antipsychotic cohorts in any glucose parameter with the exception of 1 parameter in 3 studies. In a 14-week RCT, olanzapine demonstrated a significant increase from baseline in mean glucose levels in contrast to haloperidol, clozapine, and risperidone. A categorical analysis from the same study, however, found no significant differences and showed that 6 clozapine patients, 4 olanzapine patients, and 3 risperidone patients developed abnormal fasting glucose levels greater than 6.1 mmol/L. In one further study over the course of 52 weeks, there were no between-group differences between quetiapine and haloperidol in HbA_{1c} values; however, baseline values decreased significantly in the haloperidol cohort but not in the quetiapine cohort. In a 24-week study comparing olanzapine and ziprasidone, there was a between-group difference in mean HbA_{1c} levels but not in glucose levels or categorical significant changes for any other parameter.

The most common pairing of comparators was aripiprazole and placebo. In 7 RCTs, 519 patients were randomly assigned to placebo versus an active antipsychotic comparator (commonly aripiprazole) (Table 1). The largest group of patients were randomly assigned in RCTs comparing aripiprazole and olanzapine. Four of the 22 studies compared these 2 antipsychotics alone and included 1432 patients (23% of the total database).

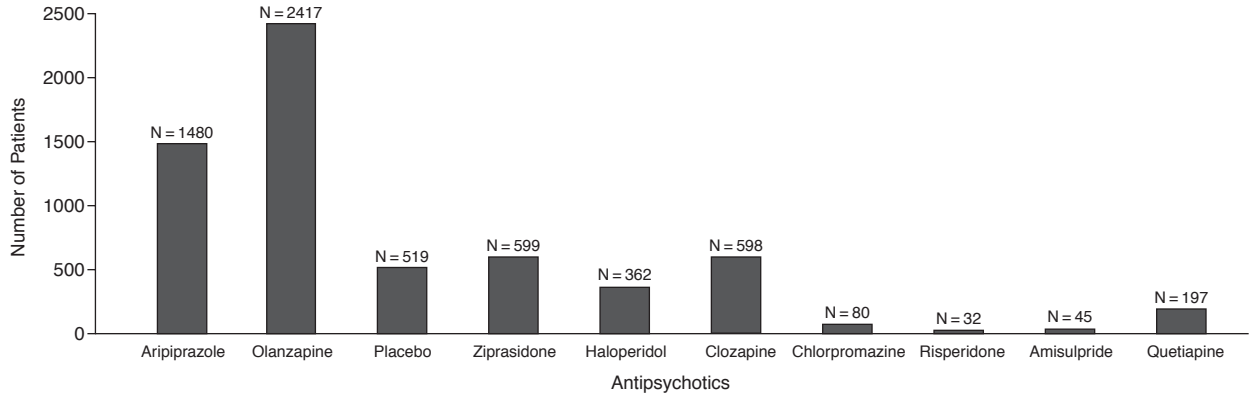
In 14 studies, data were not reported on the numbers of patients who received glucose testing, and the presumption is that all subjects were tested. In the remaining 8 studies, glucose data are reported on incomplete numbers of the original trial cohort. In some cases, differing patient numbers are reported for the cohort having mean glucose changes measured and the individual numbers having glucose levels above the upper limit of normal.

DISCUSSION

Glucose data that compare individual antipsychotic drugs and which are derived from well-conducted RCTs are currently available. In 22 clinical trials involving 6329 patients, some conducted as part of regulatory submissions, no consistent differences have been found between individual antipsychotics with regard to their association with new glucose abnormalities over trial lengths that extend up to 2 years. In 3 studies, a significant difference did emerge in a single glucose parameter, but this difference was not replicated in others.[21,27,34] In the Lindenmayer et al.[21] study, medication doses were much higher than currently recommended, and in the Kinon et al.[34] study, HbA_{1c} showed differences between olanzapine and ziprasidone, whereas other parameters did not significantly differ. There is current debate over the usage of HbA_{1c} data in nondiabetic subjects and the interpretation of these data. Although not explicitly stated in each methodology, it is likely that patients with diabetes were excluded from randomization due to protocol exclusion criteria. The consistency of these findings is in contrast to the findings from many retrospective data comparisons and pharmacovigilance studies in which nonconclusive results have emerged.[4,5,7,9,12,35–37] In the etiologic development of diabetes mellitus type 2, however, these trial lengths remain relatively short term.

To our knowledge, we authored the only other clinical article in the literature that discussed the currently available prospective glucose data that derived from RCTs, and the present article represents a significant update of the data that were available at that time.[19] The many definitions of evidence-based medicine give credence to the existence of a distinct hierarchy of levels of data. There is little disagreement between the various definitions of evidence-based medicine in that in the highest levels of

Figure 2. Numbers of Included Patients Treated With Antipsychotics



evidence, one would find meta-analyses of individual RCTs conducted to appropriate standards, systematic reviews of RCTs, and individual RCTs. These forms of data provide a higher level of evidence than retrospectively collected data (e.g., case series and case-control studies). There are many possible reasons for the lack of attention to this prospective data in many reviews and consensus statements. The data have only recently been published, and there are no references to prospective data prior to 2002. No single RCT exists in schizophrenia patients that has glucose parameters as a primary endpoint, and this must be regarded as a significant limitation of this systematic review. Furthermore, only 16 of the 22 RCTs currently report data in a peer-reviewed published article format. A good recent source of data has been the Internet. There are an increasing number of sites that publish clinical trial data that otherwise are not in the public domain. These Internet sites are in addition to the FDA Web site and the European Medicines Evaluation Agency Web site on which scientific data sets are openly available for review. Four of the RCTs have only presented their glucose data in abstracts and/or posters at major international and national congresses to date. That there is an increasing desire for glucose and other metabolic data comparing antipsychotics is evidenced by the separate presentation of the glucose data in some detail as a subsequent poster, whereas the primary publication contained minimal glucose data.[22,38] The predominant reason for the exclusion of these data from most consensus discussions is likely to be the view that study lengths are too short to demonstrate comparative diabetogenic potential. Length of treatment in the retrospective studies is often no longer than in the prospective studies, and thus any diabetogenic potential from these studies also cannot be assumed to be demonstrable within this timescale.

In classical diabetes mellitus type 2, abnormal elevations of insulin levels and measures of insulin resistance precede hyperglycemia by 5 to 10 years.[3] The cases of diabetes mellitus type 2 in these studies are thus not necessarily related to the antipsychotic medications. Even though 3 of the 22 studies reported data at 2 years, this may be too short a timescale to properly judge any possible diabetogenic potential. The literature contains data comparing insulin levels and other early markers of insulin resistance (e.g., insulin sensitivity) between antipsychotics; however, these studies tend to be cross-sectional in design and include nonobese cohorts.[39,40] Patients have, however, been treated for lengths of time (24–34 months) similar to the longest prospective studies (24 months).[40] The prospective studies evaluating insulin give conflicting results, with some data suggesting olanzapine to be associated with a reduction in insulin at 2 weeks but most data conflicting with this.[41,42] One study found that, after 6 weeks, patients treated with olanzapine had significantly higher insulin levels than patients treated with ziprasidone ($p = .051$), but the difference was no longer significant after 2 years of treatment.[15,32]

The majority of patients in this systematic review were taking aripiprazole, clozapine, ziprasidone, or olanzapine. This is reflective of aripiprazole and ziprasidone both being relatively recently licensed and the desire to make safety comparisons with olanzapine. There were, however, few patients who received typical antipsychotics, but it is of note that in a 2-year study of 263 first-episode subjects comparing haloperidol with olanzapine, no differences are reported in glucose outcomes.[31]

Of the 22 studies, 4 involve aripiprazole and olanzapine, and these form the most common active-drug comparator set, including 1432 of the total of 6329 patients in this systematic review. Aripiprazole was licensed as an antipsychotic in the United Kingdom in June 2004, and data are starting to emerge on metabolic comparisons with olanzapine. No differences emerged from the two 6-month and two 12-month studies.

The difficulty in evaluating treatment-emergent hyperglycemia in any type of study is complex. New incident cases developing in the short term are unlikely to be always associated with current treatments. In 7 of these clinical trials, a number of patients were randomly assigned to placebo, and in trials extending up to 6 months, new incident glucose abnormalities were not uncommon. It is salient to note that in none of these 7 studies was the incidence of new glucose abnormalities different between placebo and the cohort receiving an active antipsychotic. Some of this placebo cohort data have been reported in more detail in an earlier article.[19] Schizophrenia as an illness represents an independent risk factor for diabetes mellitus type 2,[43] and it has been postulated although not proven that treatment-naive patients may already have factors that predispose to the metabolic syndrome.[44–47] Some evidence suggests that increased visceral obesity, insulin resistance, elevated cortisol, and elevated glucose are present prior to antipsychotic treatments. Genetically, the link between schizophrenia and diabetes seems strong with diabetes mellitus type 2 and glycemic abnormalities being significantly more common in nonschizophrenic family members of schizophrenia patients than in the general population (17% vs. 4.6%).[3,48–52] Recent data report more abnormal oral glucose tolerance tests in first-degree relatives of schizophrenia subjects than in controls.[53]

There are 2 clinical studies that might warrant some discussion. We have included in this review an RCT of 101 schizophrenia patients randomly assigned to clozapine, haloperidol, olanzapine, and risperidone for 14 weeks.[21] This study can almost be regarded as 2 separate studies. For an initial 8-week period, patients received fixed doses of antipsychotics that could be regarded as within the Summary of Product Characteristics (SPC) limits recommended in the United Kingdom. At the end of this period, patients treated with clozapine and haloperidol experienced significant increases in glucose levels. During the subsequent 6 weeks, patients received flexible doses that led to dosages exceeding generally used dosing regimens (except clozapine)—olanzapine, mean = 31.4 (SD = 6) mg; risperidone, mean = 11.6 (SD = 3.7) mg; and haloperidol, mean = 25.8 (SD = 5.1) mg. At the end of this second period, the change in mean glucose from baseline was significantly increased only for olanzapine ($p < .02$). However, 14% (14 of 101 patients) developed abnormal glucose levels greater than 6.1 mmol/L (125 mg/dL) during the study (clozapine, 6; olanzapine, 4; risperidone, 3; and haloperidol, 1).

The second clinical trial, which has not been included in this systematic review, is the CATIE study.[14] The CATIE study is a pragmatic RCT that had all-cause discontinuation as its primary endpoint and randomly assigned 1432 patients to various antipsychotics. Although glucose measurements were included as a secondary trial endpoint, the data currently published do not allow us to incorporate the glucose data from the CATIE trial into the systematic review. There are 3 specific reasons. First, 40% of the olanzapine patients received 30 mg, as opposed to the maximal recommended dosage of 20 mg worldwide, and patients receiving other antipsychotics in general terms received dosages that approximated current United Kingdom SPC recommended limits. Second, a significant number of patients at baseline either were known to have diabetes mellitus type 2 (9%–11%) or were diagnosed on fasting glucose measurements as having an existing abnormal glucose level (25.7% of the whole cohort had fasting glucose > 5.6 mmol/L). Thus, the 2 different cohorts need to be analyzed separately. Third, the data presented include both fasting and random glucose data, in the same patient at different sampling times and in different patients. The data reported from CATIE on 1432 patients is a significantly larger cohort than the 689 patients for whom fasting metabolic parameters at baseline have been presented.[54] The interpretation of an admixture of random and fasting data falls outside of the scope of this publication.[55]

There is a great variability in the incidence of glucose abnormalities observed between the various studies. Some of this variability may be accounted for by the variable use of either random or fasting glucose as the parameter and the varying parameters used. Fasting glucose measurements are not always easy to obtain in schizophrenia patients and were only reported in 14 of the 22 studies, with random glucose measurements reported in 9 of the 22 studies (both parameters were available from 1 study). Some degree of categorical data (> 11 mmol/L random or > 6.1 mmol/L fasting or HbA_{1c}) were reported from 12 of 22 studies. However, the most common data presentation was as mean glucose change from baseline. There is current debate regarding the most appropriate glucose measurement that can be regularly measured in a schizophrenia population. Evidence suggests that oral glucose tolerance tests are not feasible as a routine test and that a single fasting glucose sample is of little greater benefit in terms of increased specificity and sensitivity than a random sample.[56] Data presented in a categorical format may intuitively be more meaningful to clinicians and patients alike in conveying any potential likelihood of a newly emergent glucose abnormality.

There are a number of significant limitations to any tentative conclusions from this systematic review. First, glucose endpoints were not a primary endpoint in any of the 22 studies. Relevant confounder's specific to glucose (for example a positive family history of diabetes mellitus type 2) would thus not have been addressed in the randomization process. No single study would have been powered to detect a specific difference between antipsychotics in their association with newly emergent glucose abnormalities. Our systematic review can only suggest a

hypothesis that needs to be addressed in an appropriate clinical trial with glucose parameters as a primary endpoint. Second, in many of the studies, data are not reported for the complete cohort for glucose parameters. No reasons are given for these omissions. Such selective sampling again introduces potential bias as it cannot be presumed that the tested cohort is similar in any respect to the nontested cohort. In some cases, the partial reporting of the data seems confusing, with varying numbers of patients within the same study providing data for different glucose parameters. Last, diabetes mellitus type 2 is in many cases a slowly developing illness with a lag time of up to 10 years between first onset of insulin resistance and abnormal glucose levels. Any trial that might wish to address the longer-term relationship between antipsychotics and glucose will be problematic to design in view of the high rates of discontinuation of patients from RCTs and the usage of other concomitant, potentially diabetogenic medications.

In summary, the relationship between schizophrenia and diabetes mellitus type 2 remains complex. In helping to unravel the causation issues, these data from 22 RCTs do provide a new data set that might not have been taken into account in the past. In the prospective RCT studies reviewed, no consistent significant differences in the incidence of glucose abnormalities were seen among patients treated with the various atypical antipsychotics. This conclusion needs to be contextualized by the relatively short-term trial lengths but is at odds with the data from the retrospective studies conducted over similar treatment lengths.

For new atypical antipsychotics in clinical development, it is important to evaluate how changes in glucose metabolism (fasting glucose, insulin, insulin sensitivity, HbA_{1c}) during longer-term treatment compare with those observed in patients treated with existing atypical antipsychotics.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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